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(54) **BI-DIRECTIONAL PARTIAL RE-BREATHING METHOD**

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(52) **U.S. Cl.** **600/504**; 600/529; 600/532; 600/484; 128/204.23

(58) **Field of Search** 600/504, 481, 600/483, 484, 485, 529, 531, 532, 533, 538; 128/200.24, 204.22, 204.23, 204.26, 205.24

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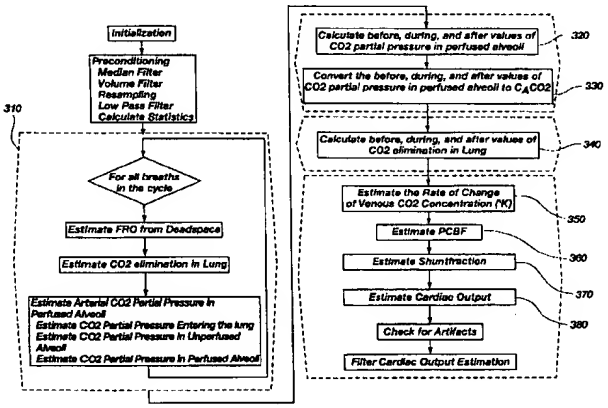
(57) **ABSTRACT**

A re-breathing method for determining pulmonary capillary blood flow that accounts for changes in the cardiac output or in the carbon dioxide content of the venous blood of a patient. The carbon dioxide elimination and partial pressure of end tidal carbon dioxide of the patient are non-invasively measured prior to re-breathing, during re-breathing, and after re-breathing. The carbon dioxide elimination and the carbon dioxide content of the alveolar blood of the patient at each of the before, during, and after re-breathing phases are then used to calculate the pulmonary capillary blood flow of the patient. A rate of change of carbon dioxide content of the venous blood of the patient may also be calculated and employed in calculating the pulmonary capillary blood flow of the patient.

38 Claims, 4 Drawing Sheets



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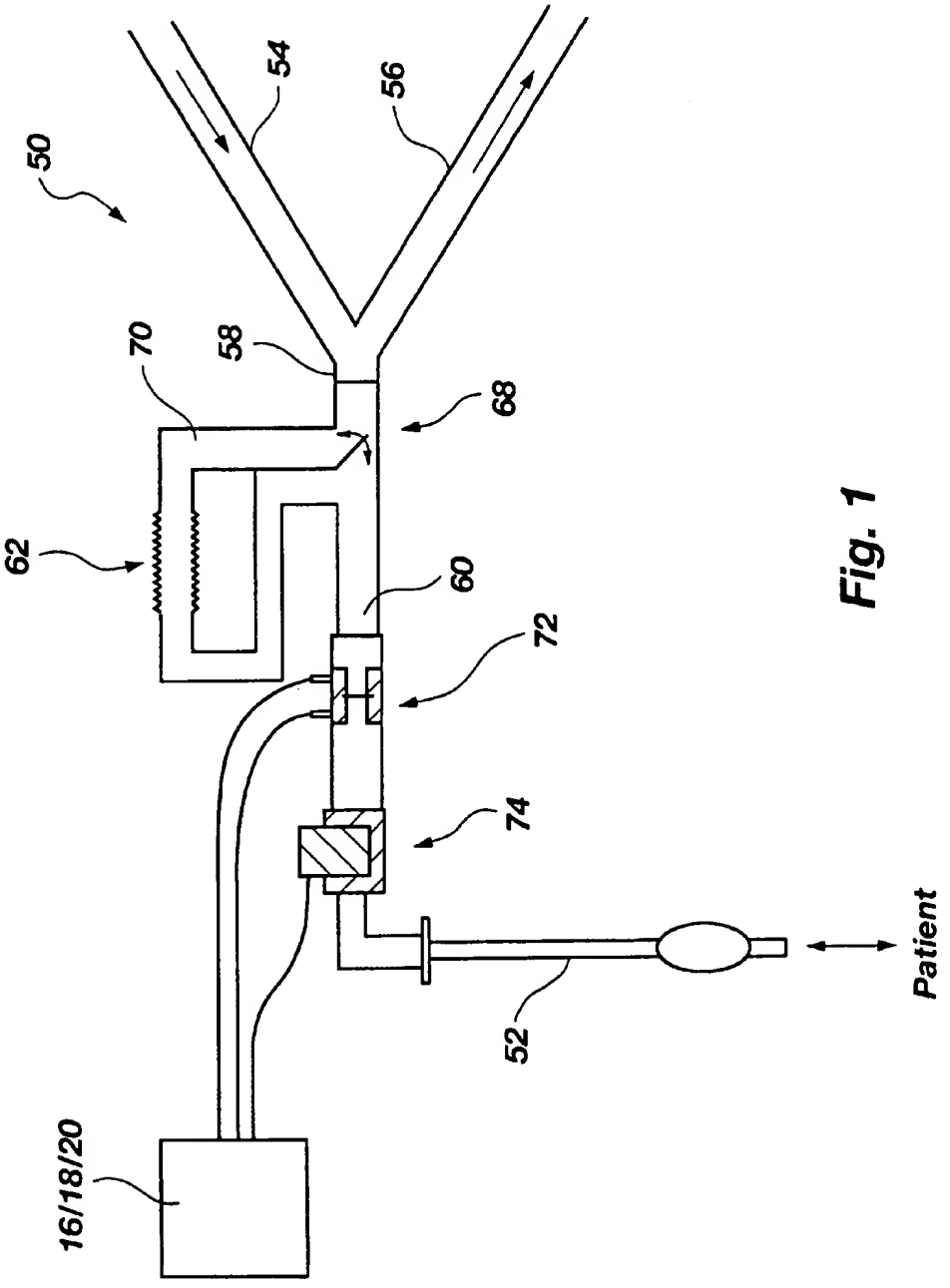

Fig. 1

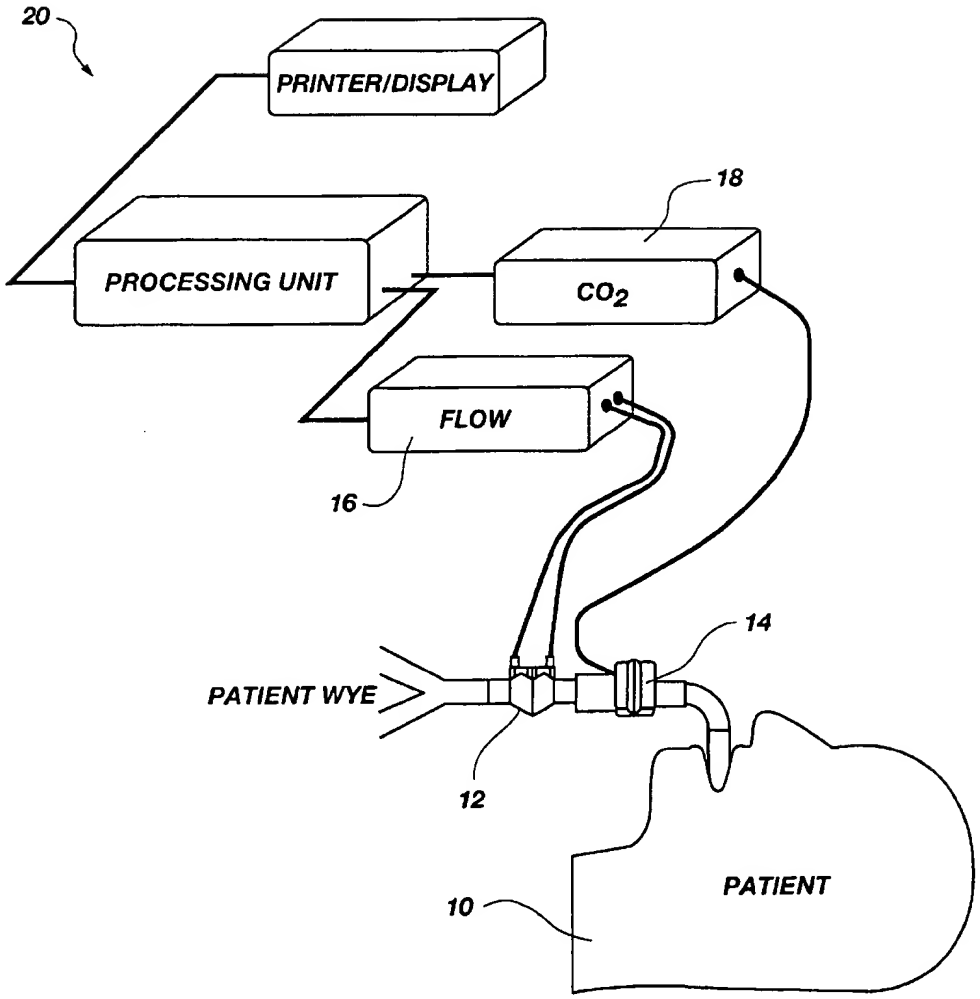
20
PRINTER/DISPLAY
18
PROCESSING UNIT
CO_2
FLOW
16
14
PATIENT WYE
12
PATIENT
10

Fig. 2

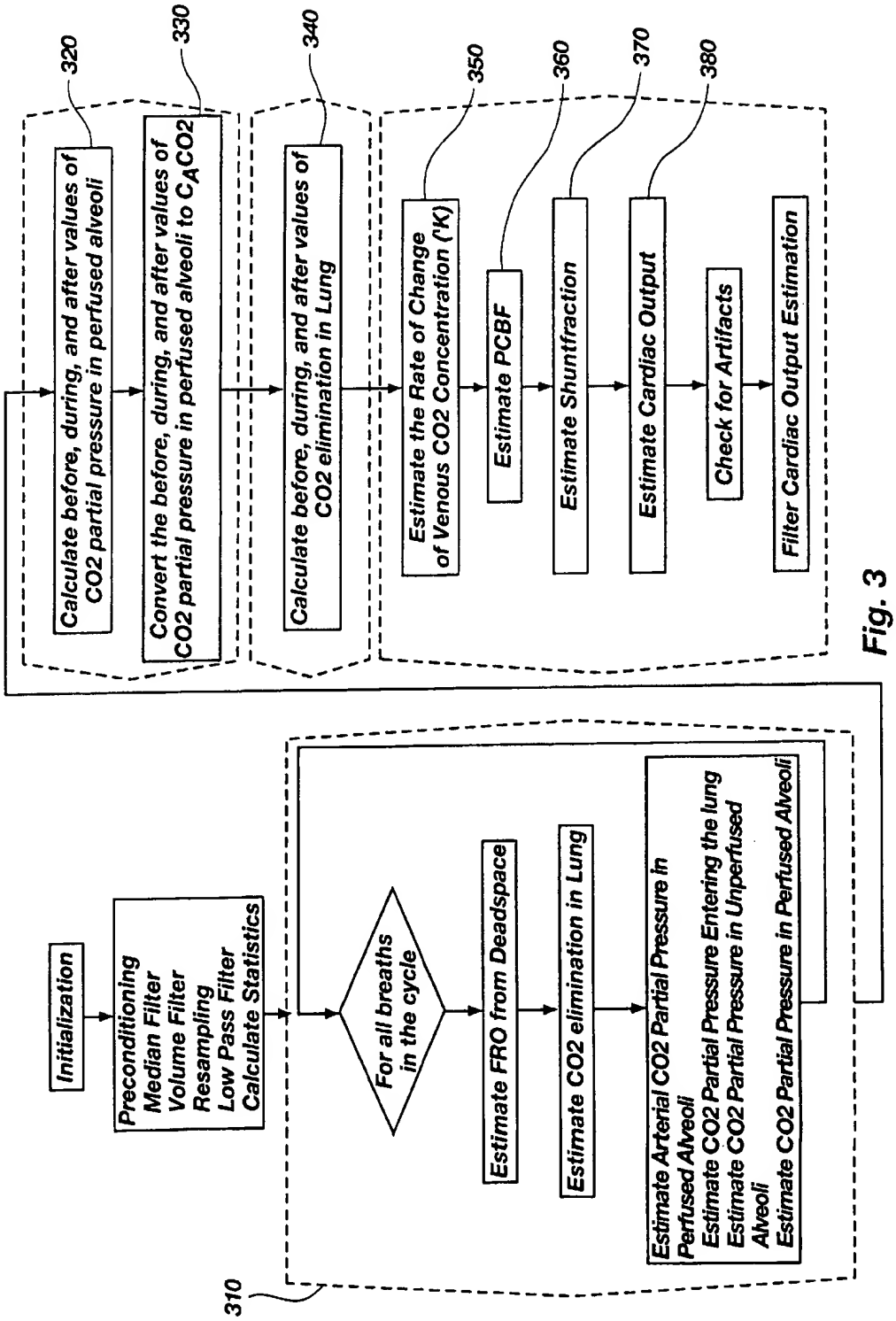
Initialization
Preconditioning
Median Filter
Volume Filter
Resampling
Low Pass Filter
Calculate Statistics
For all breaths in the cycle
Estimate FRO from Deadspace
Estimate CO2 elimination in Lung
Estimate Arterial CO2 Partial Pressure in Perfused Alveoli
Estimate CO2 Partial Pressure Entering the lung
Estimate CO2 Partial Pressure in Unperfused Alveoli
Estimate CO2 Partial Pressure in Perfused Alveoli
310
320
Calculate before, during, and after values of CO2 partial pressure in perfused alveoli
330
Convert the before, during, and after values of CO2 partial pressure in perfused alveoli to C_ACO2
340
Calculate before, during, and after values of CO2 elimination in Lung
350
Estimate the Rate of Change of Venous CO2 Concentration ('K)
360
Estimate PCBF
370
Estimate Shuntfraction
380
Estimate Cardiac Output
Check for Artifacts
Filter Cardiac Output Estimation

Fig. 3

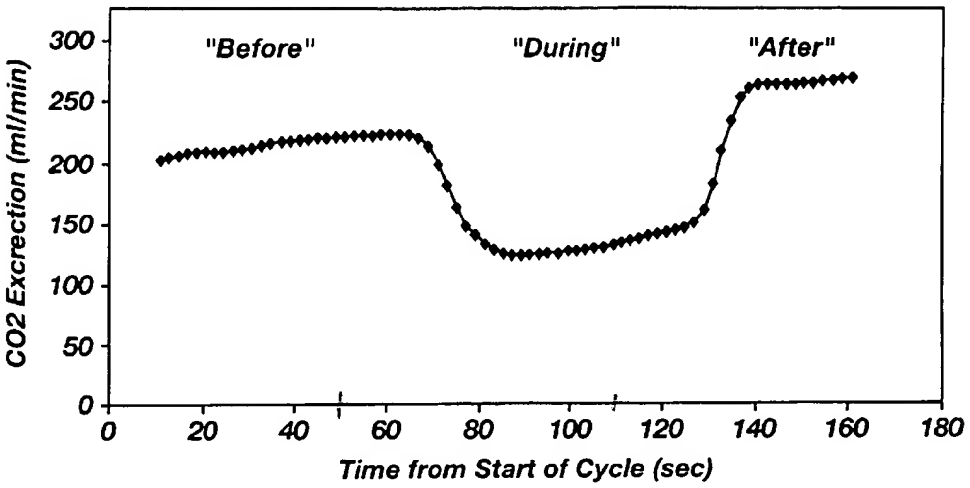
"Before"
"During"
"After"
CO2 Excrection (ml/min)
300
250
200
150
100
50
0
0
20
40
60
80
100
120
140
160
180
Time from Start of Cycle (sec)

Fig. 4

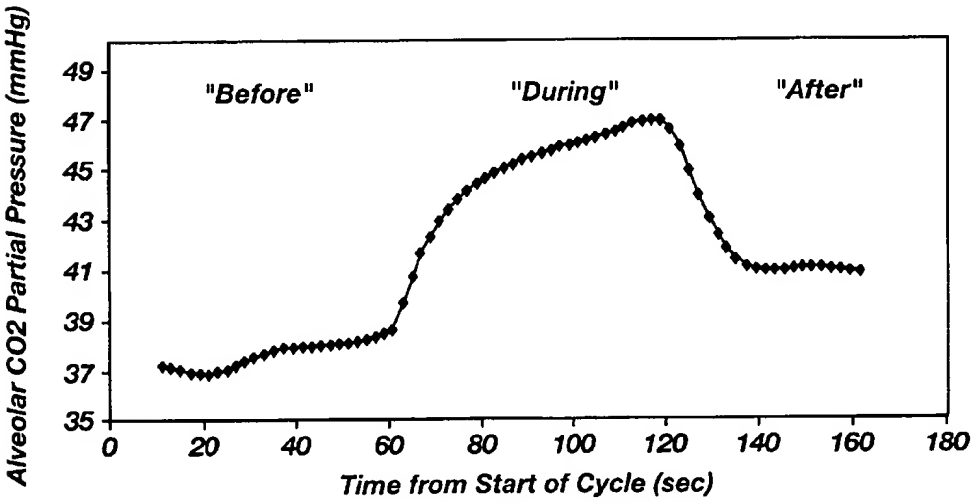
"Before"
"During"
"After"
Alveolar CO2 Partial Pressure (mmHg)
49
47
45
43
41
39
37
35
0
20
40
60
80
100
120
140
160
180
Time from Start of Cycle (sec)

Fig. 5

BI-DIRECTIONAL PARTIAL RE-BREATHING METHOD

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to methods of non-invasively determining the pulmonary capillary blood flow of a patient. Particularly, the present invention relates to re-breathing techniques for measuring the pulmonary capillary blood flow of a patient. More particularly, the methods of the present invention account for changes in the carbon dioxide content of the venous blood of a patient or in the cardiac output of a patient that may occur during re-breathing.

2. Background of Related Art

Cardiac output, the volume of blood that is pumped by the heart over a set period of time, includes two components, pulmonary capillary blood flow (Q_{pcbf}) and intrapulmonary shunt (Q_s). Pulmonary capillary blood flow is the volume of blood (typically measured in liters) that participates in the exchange of blood gases over a set period of time (typically one minute). Cardiac output is typically measured during surgery or while a patient is under intensive care, and indicates the cardiovascular condition of the patient and the patient's response to medical intervention. Conventionally, cardiac output has been measured by both invasive and non-invasive techniques.

Indicator dilution, an exemplary invasive, typically intermittent technique for measuring cardiac output, includes introducing a predetermined amount of an indicator into a single point of the bloodstream of a patient and analyzing blood downstream from the point of introduction to obtain a time vs. dilution curve. Thermodilution, in which saline solution at room temperature or a colder temperature, which may also be referred to as "cold" saline, is employed as the indicator, is a widely employed type of indicator dilution. Typically, the cold saline is introduced into the right heart bloodstream of a patient through a thermodilution catheter, which includes a thermistor at an end thereof. The thermistor is employed to measure the temperature of the blood after it has passed through the right heart, or downstream from the point at which the cold saline is introduced. A thermodilution curve is then generated from the data, from which the cardiac output of the patient may be derived. Thermodilution and other indicator dilution techniques are, however, somewhat undesirable due to the potential for harm to the patient that is associated by inserting and maintaining such catheters in place.

Conventional, so-called "non-invasive" techniques for determining the cardiac output of a patient typically include a pulmonary capillary blood flow measurement according to the Fick principle: the rate of uptake of a substance by or release of a substance from blood at the lung is equal to the blood flow past the lung and the content difference of the substance at each side of the lung. The Fick principle may be represented in terms of oxygen (O_2) by the following formula:

$$Q=Vo_2/(CaO_2-CvO_2),$$

where Q is the cardiac output of the patient, Vo_2 is the volume of oxygen consumed by the patient per unit of time, CaO_2 is the O_2 content of the arterial, or oxygenated, blood of the patient, and CvO_2 is the O_2 content of the venous, or de-oxygenated, blood of the patient. The oxygen Fick principle may be employed in calculating the cardiac output of a patient either intermittently or continuously. The intrapulmonary shunt flow may also be estimated, and subtracted from the cardiac output to determine the pulmonary capillary blood flow of the patient.

An exemplary method of determining the cardiac output of a patient by monitoring Vo_2 is disclosed in Davies et al., Continuous Fick cardiac output compared to thermodilution cardiac output, *Crit. Care Med.* 1986; 14:881–885 ("Davies"). The method of Davies includes continually measuring the O_2 content of samples of gas inspired and expired by a patient, the oxygen saturation (SvO_2) of the patient's venous blood, and oxygen saturation (SaO_2) of the patient's arterial blood. The O_2 measurements are made by a metabolic gas monitor, and Vo_2 calculated from these measurements. SaO_2 is measured by pulse oximetry. SvO_2 is directly measured by a pulmonary artery ("PA") catheter. Each of these values is then incorporated into the oxygen Fick equation to determine the cardiac output of the patient. Although the method of Davies may be employed to intermittently or continuously determine the cardiac output of a patient, it is somewhat undesirable from the standpoint that accurate Vo_2 measurements are typically difficult to obtain, especially when the patient requires an elevated fraction of inspired oxygen (Fio_2). Moreover, since the method disclosed in Davies requires continual measurement of SvO_2 with a pulmonary artery catheter, it is an invasive technique.

Due in part to the ease with which the carbon dioxide elimination (Vco_2) of a patient may be accurately measured, Vco_2 measurements may be employed in methods of non-invasively determining the pulmonary capillary blood flow of a patient. Since the respiratory quotient (RQ) is the ratio of carbon dioxide elimination to the amount of oxygen inhaled, Vco_2 may be substituted for Vo_2 according to the following equation:

$$Vo_2=Vco_2/RQ.$$

Alternatively, a modification of the Fick principle, which is based on the exchange of carbon dioxide (CO_2) in the lungs of a patient, has been employed to calculate the pulmonary capillary blood flow of the patient. The carbon dioxide Fick equation, which represents the Fick principle in terms of CO_2 elimination and exchange, follows:

$$Q=Vco_2/(CvCO_2-CaCO_2),$$

where Vco_2 is the carbon dioxide elimination of the patient, $CvCO_2$ is the content, or concentration, of CO_2 in the venous blood of the patient, and $CaCO_2$ is the content, or concentration, of CO_2 in the arterial blood of the patient. The difference between $CvCO_2$ and $CaCO_2$ is typically referred to as the arterial-venous gradient, or "AV gradient".

The carbon dioxide Fick equation has been employed to non-invasively determine the pulmonary capillary blood flow and cardiac output of a patient on an intermittent basis. The carbon dioxide elimination of the patient may be non-invasively measured as the difference per breath between the volume of carbon dioxide inhaled during inspiration and the volume of carbon dioxide exhaled during expiration, and is typically calculated as the integral of the carbon dioxide signal times the rate of flow over an entire breath. The volume of carbon dioxide inhaled and exhaled may each be corrected for any deadspace.

The partial pressure of end-tidal carbon dioxide ($PetCO_2$ or $etCO_2$) is also measured in re-breathing processes. The partial pressure of end tidal carbon dioxide, after correcting for any deadspace, is typically assumed to be approximately equal to the partial pressure of carbon dioxide in the alveoli

($PaCO_2$) of the patient or, if there is no intrapulmonary shunt, the partial pressure of carbon dioxide in the arterial blood of the patient ($PaCO_2$).

Re-breathing is typically employed either to non-invasively estimate the carbon dioxide content of mixed venous blood (in total re-breathing) or to obviate the need to know the carbon dioxide content of the mixed venous blood (by partial re-breathing). Re-breathing processes typically include the inhalation of a gas mixture which includes carbon dioxide. During re-breathing, the CO_2 elimination of the patient is less than during normal breathing. Re-breathing during which the CO_2 elimination decreases to near zero is typically referred to as total re-breathing. Re-breathing that causes some decrease, but not a total cessation of CO_2 elimination, is typically referred to as partial re-breathing.

Re-breathing is typically conducted with a re-breathing circuit, which causes a patient to inhale a gas mixture that includes carbon dioxide. FIG. **1** schematically illustrates an exemplary re-breathing circuit **50** that includes a tubular airway **52** that communicates air flow to and from the lungs of a patient. Tubular airway **52** may be placed in communication with the trachea of the patient by known intubation processes, or by connection to a breathing mask positioned over the nose and/or mouth of the patient. A flow meter **72**, which is typically referred to as a pneumotachometer, and a carbon dioxide sensor **74**, which is typically referred to as a capnometer, are disposed between tubular airway **52** and a length of hose **60**, and are exposed to any air that flows through re-breathing circuit **50**. Both ends of another length of hose, which is referred to as deadspace **70**, communicate with hose **60**. The two ends of deadspace **70** are separated from one another by a two-way valve **68**, which may be positioned to direct the flow of air through deadspace **70**. Deadspace **70** may also include an expandable section **62**. A Y-piece **58**, disposed on hose **60** opposite flow meter **72** and carbon dioxide sensor **74**, facilitates the connection of an inspiratory hose **54** and an expiratory hose **56** to re-breathing circuit **50** and the flow communication of the inspiratory hose **54** and expiratory hose **56** with hose **60**. During inhalation, gas flows into inspiratory hose **54** from the atmosphere or a ventilator (not shown). During normal breathing, valve **68** is positioned to prevent inhaled and exhaled air from flowing through deadspace **70**. During re-breathing, valve **68** is positioned to direct the flow of exhaled and inhaled gases through deadspace **70**.

During total re-breathing, substantially all of the gas inhaled by the patient was expired during the previous breath. During total re-breathing, the partial pressure of end-tidal carbon dioxide is typically assumed to be equal to the partial pressure of carbon dioxide in the venous blood ($PvCO_2$) of the patient, as well as to the partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) and the partial pressure of carbon dioxide in the alveolar blood ($PACO_2$) of the patient. Total re-breathing processes are based on the assumption that neither pulmonary capillary blood flow nor the content of carbon dioxide in the venous blood of the patient ($CvCO_2$) change substantially during the re-breathing process. The partial pressure of carbon dioxide in blood may be converted to the content of carbon dioxide in blood by means of a carbon dioxide dissociation curve. The carbon dioxide form of the Fick equation, in which $CvCO_2$ and $CaCO_2$ are variables, may be employed to determine pulmonary capillary blood flow.

In partial re-breathing, the patient inhales a mixture of gases exhaled during the previous breath and "fresh" gases. Thus, the patient does not inhale as much carbon dioxide as would be inhaled during a total re-breathing process. Conventional partial re-breathing processes typically employ a differential form of the carbon dioxide Fick equation to determine the pulmonary capillary blood flow of the patient, which does not require knowledge of the carbon dioxide content of the mixed venous blood. This differential form of the carbon dioxide Fick equation considers measurements of carbon dioxide elimination (Vco_2), $CvCO_2$, and the content of carbon dioxide in the alveolar blood of the patient ($CaCO_2$) during both normal breathing and the re-breathing process as follows:

$$Q_{pcbfBD} = \frac{V_{CO_{2B}} - V_{CO_{2D}}}{(CvCO_{2B} - CvCO_{2D}) - (C_ACO_{2B} - C_ACO_{2D})},$$

where $Vco_{2\,B}$ and $Vco_{2\,D}$ are the carbon dioxide elimination of the patient before re-breathing and during the re-breathing process, respectively, $CvCO_{2\,B}$ and $CvCO_{2\,D}$ are the contents of CO_2 of the venous blood of the patient before re-breathing and during the re-breathing process, respectively, and $CaCO_{2\,B}$ and $CaCO_{2\,D}$ are the contents of CO_2 in the alveolar blood (i.e., the blood in the capillaries that surround the alveoli) of the patient before re-breathing and during the re-breathing process, respectively. The alveolar partial pressures of carbon dioxide may then be converted to the carbon dioxide contents of the patient's alveolar blood by means of a carbon dioxide dissociation curve. During conventional re-breathing processes, the pulmonary capillary blood flow and $CvCO_2$ of a patient are assumed to remain substantially unchanged. The latter assumption causes the $CvCO_2$ terms of the preceding equation to cancel each other, but is somewhat undesirable because it may introduce error into the cardiac output determination since $CvCO_2$ may change during re-breathing.

Alternative differential Fick methods of measuring pulmonary capillary blood flow or cardiac output have also been employed. Such differential Fick methods typically include a brief change of $PetCO_2$ and Vco_2 in response to a change in effective ventilation. This brief change can be accomplished by adjusting the respiratory rate, inspiratory and/or expiratory times, or tidal volume. A brief change in effective ventilation may also be effected by adding CO_2, either directly or by re-breathing. An exemplary differential Fick method that has been employed, which is disclosed in Gedeon, A. et al. in 18 *Med. & Biol. Eng. & Comput.* 411–418 (1980), employs a period of increased ventilation followed immediately by a period of decreased ventilation.

Cardiac output, which is also assumed to remain constant in many conventional re-breathing techniques, may also change during re-breathing. In fact, changes in cardiac output during re-breathing are known to be more common than changes in $CvCO_2$. As with the undesirability of the assumption that $CvCO_2$ remains constant during re-breathing, the assumption that cardiac output is constant may lead to inaccuracies in the cardiac output determination.

Accordingly, an accurate, non-invasive method of determining the pulmonary capillary blood flow or cardiac output of a patient is needed that compensates for changes in the carbon dioxide content of the venous blood of a patient during re-breathing or for changes in the cardiac output of the patient during re-breathing.

SUMMARY OF THE INVENTION

The re-breathing method of the present invention includes determining the volume of carbon dioxide exhaled by a patient which estimates the carbon dioxide elimination

(VCO_2) of the patient, before $VCO_{2\,B}$) during ($VCO_{2\,D}$) and after ($VCO_{2\,A}$) either total or partial re-breathing. The end tidal partial pressure of carbon dioxide is also measured for each of the "before", "during" and "after" phases. From the end tidal partial pressures, the partial pressure of carbon dioxide in the alveoli of the lungs of the patient that participate in the exchange of oxygen for carbon dioxide in the blood, which are typically referred to as "perfused" alveoli, is determined. A carbon dioxide dissociation curve is employed with the end tidal carbon dioxide partial pressure measurements, as known in the art, to convert these partial pressures to the content of carbon dioxide in the blood of the "exit" end of capillaries that surround the perfused alveoli ($Cc'CO_2$), which is typically referred to as the "end-capillary" blood, for each of the "before", "during" and "after" phases.

The differences between the carbon dioxide elimination before re-breathing and during re-breathing, which difference is also referred to as "$\Delta CO_{2\,BD}$", and during re-breathing and after re-breathing, which difference is also referred to as "$\Delta VCO_{2\,DA}$", are determined. The differences between the content of end capillary carbon dioxide in the capillary blood before and during re-breathing, which difference is also referred to as "$\Delta CACO_{2\,BD}$", and during re-breathing and after re-breathing, which difference is also referred to as "$\Delta CACO_{2\,DA}$", are also determined.

These differences are then employed to calculate the rate at which the content of carbon dioxide in the venous blood of the patient changes. An exemplary equation for estimating the rate of change in the content of carbon dioxide in the patient's venous blood (k), which assumes that the change is linear with time and, therefore, that the rate of change is constant, or the change is linear with respect to time, follows:

$$k = \frac{\Delta V_{CO_{2BD}} \cdot \Delta C_A CO_{2DA} - \Delta V_{CO_{2DA}} \cdot \Delta C_A CO_{2BD}}{\Delta V_{CO_{2BD}}(t_D - t_A) - \Delta V_{CO_{2DA}}(t_B - t_D)},$$

Alternatively, the change in carbon dioxide content in the venous blood may be assumed to follow a curve of some other shape that is reasonably based on the character of the change in carbon dioxide content and that could be approximated by methods such as an exponential curve, or the curve of a polynomial, an artificial neural network, or a radial basis function.

Once the rate of change in the content of carbon dioxide in the patient's blood has been estimated, the pulmonary capillary blood flow (Q_{pcbf}) of the patient may be accurately determined as follows:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2V_{CO_{2D}}}{k \cdot (t_B + t_A - 2t_D) - (C_A CO_{2B} + C_A CO_{2A} - 2C_A CO_{2D})},$$

where t_B, t_D and t_A represent the times at which VCO_2 and $CACO_2$ were determined during the "before", "during" and "after" phases, respectively.

In a more simple form of the previous equation, the constant and time elements may be omitted to provide an equation with which the Q_{pcbf} of the patient may be accurately determined:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - (2V_{CO_{2D}})}{-(C_A CO_{2B} + C_A CO_{2A} + 2C_A CO_{2D})},$$

The methods of the present invention may also be applied to alternative differential Fick methods of measuring pulmonary capillary blood flow or cardiac output, which require a brief change of $PetCO_2$ and VCO_2 in response to a change in effective ventilation. This brief change in effective ventilation can be accomplished by adjusting the respiratory rate, inspiratory and/or expiratory times, or tidal volume. A brief change in effective ventilation may also be effected by adding CO_2, either directly or by re-breathing. An exemplary differential Fick method, which is disclosed in Gedeon, A. et al. in 18 *Med. & Biol. Eng. & Coinput.* 411–418 (1980), employs a period of increased ventilation followed immediately by a period of decreased ventilation.

Other features and advantages of the present invention will become apparent through a consideration of the ensuing description, the accompanying drawings, and the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic representation of an exemplary re-breathing circuit that may be employed with the methods of the present invention;

FIG. **2** is a schematic representation which illustrates the componentry that may be utilized to measure respiratory profile parameters that are employed in the methods of the present invention;

FIG. **3** is a flow chart that schematically illustrates the method of the present invention;

FIG. **4** is a line graph that illustrates the VCO_2 of a patient during each of the before, during, and after phases of the re-breathing method of the present invention; and

FIG. **5** is a line graph that illustrates the $etCO_2$ of a patient during each of the before, during, and after phases of the re-breathing method of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention includes a method of non-invasively determining the pulmonary capillary blood flow or the cardiac output of a patient. In a first embodiment of the method, which is useful when the carbon dioxide content of the venous blood of a patient ($CvCO_2$) is changing, the rate at which the $CvCO_2$ changes is estimated. The rate of change may be employed to determine the amount of change in the carbon dioxide content of the venous blood of the patient or the pulmonary capillary blood flow of the patient. Formulae are employed in accordance with the method of the present invention to determine the rate of change in the carbon dioxide content of the venous blood of the patient, the amount of change in the carbon dioxide content, and the pulmonary capillary blood flow.

Alternatively, in a second embodiment of the method of the present invention, pulmonary capillary blood flow or cardiac output may be determined without estimating the rate of change in $CvCO_2$. The second embodiment of the present invention is useful for determining the pulmonary capillary blood flow or cardiac output of a patient when either $CvCO_2$ or cardiac output changes during the re-breathing process.

Derivation of Formulae Employed in the Methods

A differential form of the carbon dioxide Fick equation, similar to that employed in conventional partial re-breathing techniques, which is based on carbon dioxide elimination and venous CO_2 content measurements taken before

re-breathing, during normal breathing, and during the re-breathing process, follows:

$$Q_{pcbfBD} = \frac{V_{CO_{2B}} - V_{CO_{2D}}}{(CvCO_{2B} - CvCO_{2D}) - (C_ACO_{2B} - C_ACO_{2D})} \quad (1)$$

$$Q_{pcbfBD} = \frac{\Delta V_{CO_{2BD}}}{\Delta CvCO_{2BD} - \Delta C_ACO_{2BD}},$$

where $CvCO_{2\ B}$ is the CO_2 content of the venous blood of the patient prior to re-breathing, or in the "before" phase, and $CvCO_{2\ D}$ is the CO_2 content of the venous blood of the patient during re-breathing, or in the "during" phase.

Another differential form of the carbon dioxide Fick equation, which is based on carbon dioxide elimination and CO_2 content measurements made during the re-breathing process and after re-breathing, which may also be employed to determine the pulmonary capillary blood flow of a patient, follows:

$$Q_{pcbfDA} = \frac{V_{CO_{2D}} - V_{CO_{2A}}}{(CvCO_{2D} - CvCO_{2A}) - (C_ACO_{2D} - C_ACO_{2A})} \quad (2)$$

$$Q_{pcbfDA} = \frac{\Delta V_{CO_{2DA}}}{\Delta CvCO_{2DA} - \Delta C_ACO_{2DA}}, \quad (3)$$

where $CvCO_{2\ A}$ is the CO_2 content of the venous blood of the patient after re-breathing, or in the "after" phase.

The two preceding differential forms of the carbon dioxide Fick equation may be combined to yield the following differential form of the carbon dioxide Fick equation:

$$Q_{pcbf} = \frac{\Delta V_{CO_{2BD}} - \Delta V_{CO_{2DA}}}{(\Delta CvCO_{2BD} - \Delta CvCO_{2DA}) - (\Delta C_ACO_{2BD} - \Delta C_ACO_{2DA})}. \quad (4)$$

Since $CvCO_2$ may change over time, an accurate non-invasive Fick-based determination of the pulmonary capillary blood flow of a patient should include an estimation of the rate at which $CvCO_2$ changes. With an exemplary assumption that changes in $CvCO_2$ are substantially linear over the re-breathing cycle and, therefore, that the rate of change is constant, the rate of change in $CvCO_2$ (k) may be represented by the following equation:

$$k = \frac{\Delta CvCO_2}{\Delta t}. \quad (5)$$

Alternatively, the change in carbon dioxide content of the venous blood may be assumed to substantially follow a curve of some other shape that is reasonably based on the character of the change in carbon dioxide content, such as an exponential curve, wherein the rate of change would also be exponential, or the curve of a polynomial. As another alternative, the rate of change in the content of carbon dioxide in the venous blood may be approximated by an artificial neural network or a radial basis function, as known in the art.

When the change in $CvCO_2$ is assumed to be linear with respect to time and, therefore, the rate of change of $CvCO_2$ is assumed to be constant, the change in $CvCO_2$ between the "before" and "during" phases and between the "during" and "after" phases can be expressed by the following equations:

$$\Delta CvCO_{2\ BD} = k(t_B - t_D) \quad (6)$$

and

$$\Delta CvCO_{2\ DA} = k(t_D - t_A), \quad (7)$$

where t_D, t_B and t_A represent the times at which the "before", "during" and "after" phases respectively occur.

The foregoing equations for the change in $CvCO_2$ may be substituted into the differential fote of the carbon dioxide Fick equation that considers the breathing of a patient during each of the "before", "during" and "after" phases and the "Δ" terms expanded to yield the following form of the carbon dioxide Fick equation, which accounts for any changes in $CvCO_2$ and is, therefore, useful in the methods of the present invention:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2 \cdot V_{CO_{2D}}}{k \cdot (t_B + t_A - 2 \cdot t_D) - (C_ACO_{2B} + C_ACO_{2A} - 2 \cdot C_ACO_{2D})}. \quad (8)$$

If, however, $t_D - t_B = t_A - t_D$, then $t_A + t_B = 2 \cdot t_D$, and it would not be necessary to calculate k, as k would be multiplied by zero. Accordingly, if $t_D - t_B = t_A - t_D$, the following equation could be employed to determine the pulmonary capillary blood flow of a patient:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2 \cdot V_{CO_{2D}}}{-(C_ACO_{2B} + C_ACO_{2A} - 2 \cdot C_ACO_{2D})}. \quad (9)$$

Due to the assumption that the pulmonary capillary blood flow of a patient remains substantially constant from the "before" phase to the "after" phase, the differential carbon dioxide Fick equations for determining cardiac output over the "before" and "during" phases ($Q_{pcbf\ BD}$) and for determining cardiac output over the "during" and "after" phases ($Q_{pcbf\ DA}$) may be employed to estimate k, the rate of change in $CvCO_2$, as follows:

$$Q_{pcbf\ BD} = Q_{pcbf\ DA}, \quad (10)$$

thus,

$$\frac{\Delta V_{CO_{2BD}}}{\Delta CvCO_{2BD} - \Delta C_ACO_{2BD}} = \frac{\Delta V_{CO_{2DA}}}{\Delta CvCO_{2DA} - \Delta C_ACO_{2DA}}, \quad (11)$$

which may be rearranged as:

$$\Delta Vco_{2\ BD} \cdot \Delta CvCO_{2\ DA} - \Delta Vco_{2\ DA} \cdot \Delta CvCO_{2\ BD} = \Delta Vco_{2\ BD} \cdot \Delta CaCO_{2\ DA} - \Delta Vco_{2\ DA} \cdot \Delta CaCO_{2\ BD}. \quad (12)$$

The equations for $\Delta CvCO_{2\ BD}$ and $\Delta CvCO_{2\ BD}$ are then substituted into the preceding equation to yield the following equation:

$$\Delta Vco_{2\ BD} \cdot k(t_D - t_A) - \Delta Vco_{2\ DA} \cdot k(t_B - t_D) = \Delta Vco_{2\ BD} \cdot \Delta CaCO_{2\ DA} - \Delta Vco_{2\ DA} \cdot \Delta CaCO_{2\ BD}, \quad (13)$$

which may be rearranged to provide the following equation for k, the rate of change in Vco_2:

$$k = \frac{\Delta V_{CO_{2BD}} \cdot \Delta C_ACO_{2DA} - \Delta V_{CO_{2DA}} \cdot \Delta C_ACO_{2BD}}{\Delta V_{CO_{2BD}}(t_D - t_A) - \Delta V_{CO_{2DA}}(t_B - t_D)}. \quad (14)$$

Use of the Bi-Directional Re-Breathing Technique While Cardiac Output is Changing to Noninvasively Determine Pulmonary Capillary Blood

Equation (9) above may also be used to determine the pulmonary capillary blood flow of a patient if the cardiac

output of the patient changes during the bi-directional re-breathing process of the present invention. This can be shown by assuming that $CvCO_2$ does not change during re-breathing:

$$CvCO_2=CvCO_{2\,B}=CvCO_{2\,D}=CvCO_{2\,A}. \quad (15)$$

The Fick equation can be used to express carbon dioxide elimination (Vco_2) in terms of the contents of carbon dioxide in the veins ($CvCO_2$) and in the arteries ($CaCO_2$) or in the capillaries surrounding the alveoli ($CACO_2$) during each of the before, during, and after phases of the bi-directional partial re-breathing method of the present invention:

$$Vco_{2\,B}=Q_B(CvCO_{2\,B}-CACO_{2\,B}); \quad (16)$$

$$Vco_{2\,D}=Q_D(CvCO_{2\,D}-CACO_{2\,D}); \text{ and} \quad (17)$$

$$Vco_{2\,A}=Q_A(CvCO_{2\,A}-CACO_{2\,A}). \quad (18)$$

Substituting equations (16)–(18) for the $Vco_{2\,B}$, $Vco_{2\,D}$, and $Vco_{2\,A}$ terms of equation (9) along with the assumption that $CvCO_2$ is not changing during re-breathing in equation (15) provides the following equation:

$$Q=\frac{Q_B(CvCO_2-C_ACO_{2B})+Q_D(CvCO_2-C_ACO_{2D})-2Q_A(CvCO_2-C_ACO_{2A})}{-(C_ACO_{2B}+C_ACO_{2A}-2\cdot C_ACO_{2D}).} \quad (19)$$

When it is assumed that $CvCO_2$ does not change during re-breathing, it may be implied that once the re-breathing process is stopped, $CaCO_2$ and $CACO_2$ return to substantially the same levels of these parameters prior to the re-breathing process, or the same levels of these parameters if re-breathing had not been conducted or another change in the ventilation of a patient had not been induced:

$$CACO_{2\,B}=CACO_{2\,A}=CACO_{2\,NR}, \quad (20)$$

where $CACO_{2\,NR}$ is the content of carbon dioxide in the capillaries surrounding the alveoli during time periods in which a change in the ventilation of a patient has not been induced (e.g., as is induced during re-breathing). Thus, $CACO_{2\,NR}$ may be substituted for both $CACO_{2\,B}$ and $CACO_{2\,A}$ in equation (20), providing the following equation:

$$Q=\frac{Q_B\cdot CvCO_2-Q_B\cdot C_ACO_{2NR}+Q_A\cdot CvCO_2-Q_A\cdot C_ACO_{2NR}-2Q_D\cdot CvCO_2+Q_D\cdot C_ACO_{2D}}{-2(C_ACO_{2NR}-C_ACO_{2D}).} \quad (21)$$

By factoring certain terms, equation (21) can be rewritten as follows:

$$Q=\frac{(Q_B+Q_A-2Q_D)\cdot CvCO_2-(Q_A+Q_B)\cdot C_ACO_{2NR}+2Q_D\cdot C_ACO_{2D}}{-2(C_ACO_{2NR}-C_ACO_{2D}).} \quad (22)$$

If it is assumed that the cardiac output of the patient changes linearly over time, or that the difference in cardiac output between before and during phases of the bi-directional partial re-breathing method is equal to the difference in cardiac output between the during and after phases, then the cardiac output of the patient in the during phase or re-breathing may be expressed by the following equation:

$$Q_D=\tfrac{1}{2}(Q_A+Q_B). \quad (23)$$

Substituting equation (23) into equation (22) provides the following equation:

$$Q=[Q_A+Q_B-(Q_A+Q_B)]\cdot\frac{CvCO_2-(Q_A+Q_B)\cdot C_ACO_{2NR}+2C_ACO_{2D}(QA+QB)}{-2(C_ACO_{2NR}-C_ACO_{2D}),} \quad (22)$$

which is the equivalent of the following equation:

$$Q=\tfrac{1}{2}(Q_A+Q_B), \quad (23)$$

which is equal to Q_D.

Thus, when the cardiac output of a patient changes at a constant rate during the bi-directional partial re-breathing method of the present invention, the cardiac output or pulmonary capillary blood flow of a patient is equal to the cardiac output or pulmonary capillary blood flow of the patient as measured in the during phase of partial re-breathing, Accordingly, equations (8) and (9) may be used with the bi-directional partial re-breathing process of the present invention to accurately and non-invasively determine the pulmonary capillary blood flow or the cardiac output of a patient while the cardiac output of the patient is changing.

The bi-directional partial re-breathing method of the present invention, as embodied in equations (8) and (9), may also be useful for non-invasively determining the pulmonary capillary blood flow of a patient while both the $CvCO_2$ and the cardiac output of the patient are changing.

Measuring Respiratory Blood and Blood Gas Profile Parameters

With reference to FIG. **2**, a preferred embodiment of the method of the present invention includes non-invasively measuring the flow rates and carbon dioxide (CO_2) fraction of gas mixtures (e.g., air) that are inhaled and exhaled by a patient **10** over the course of the patient's breathing while known re-breathing techniques are employed. A flow sensor **12** of a known type, such as the differential-pressure type respiratory flow sensors manufactured by Novametrix Medical Systems Inc. (hereinafter "Novametrix") of Wallingford, Connecticut (e.g, the Pediatric/Adult Flow Sensor (Catalog No. 6717) or the Neonatal Flow Sensor (Catalog No. 6718)), as well as respiratory flow sensors based on other operating principles and manufactured or marketed by Novametrix or others, which may be operatively attached to a ventilation apparatus (not shown), may be employed to measure the flow rates of the breathing of patient **10**. A CO_2 sensor **14**, such as the CAPNOSTAT® CO_2 sensor and a complementary airway adapter (e.g., the Pediatric/Adult Single Patient Use Airway Adapter (Catalog No. 6063), the Pediatric/Adult Reusable Airway Adapter (Catalog No. 7007), or the Neonatal/Pediatric Reusable Airway Adapter (Catalog No. 7053)), which are manufactured by Novametrix, as well as other main stream or side stream CO_2 sensors manufactured or marketed by Novametrix or others, may be employed to measure the CO_2 fraction of gas mixtures that are inhaled and exhaled by patient **10**. Flow sensor **12** and CO_2 sensor **14** are connected to a flow monitor **16** and a CO_2 monitor **18**, respectively, each of which may be operatively associated with a computer **20** so that data from the flow and CO_2 monitors **16** and **18**, representative of the signals from each of flow sensor **12** and CO_2 sensor **14**, may be detected by computer **20** and processed according to programming (e.g., by software) thereof. Preferably, raw flow and CO_2 signals from the flow monitor and CO_2 sensor are filtered to remove

any significant artifacts. As several respiratory flow and CO_2 pressure measurements are made, the respiratory flow and CO_2 pressure data may be stored by computer **20**. Thus, cardiac output may be calculated by computer **20**, in accordance with the carbon dioxide Fick equation or by any other suitable equation known in the art.

Each breath, or breathing cycle, of patient **10** may be delineated, as known in the art, such as by continually monitoring the flow rate of the breathing of patient **10**.

The patient's breathing is monitored before re-breathing, during re-breathing, and after re-breathing, which are also referred to as the "before", "during" and "after" phases, respectively. FIG. **1** illustrates an exemplary apparatus that may be employed in re-breathing processes to detect the amount of CO_2 exhaled by the patient, from which VCO_2 and $CvCO_2$ may be determined.

When the breathing of a patient **10** (see FIG. **2**) is monitored before re-breathing, two-way valve **68** is positioned to prevent the flow of inhaled and exhaled gas through deadspace **70**. The duration of the "before" phase is preferably sufficient to obtain accurate CO_2 and flow measurements. The time at which the "before" phase occurs (t_B) is also determined. t_B may be calculated as the average time of the "before" phase, or otherwise, as known in the art. As an example, if t_B were the average time of the "before" phase, and the "before" phase started about 40 seconds after the initiation (t_0) of a re-breathing measurement and lasted until about 46 seconds after t_0, t_B would be at about 43 seconds.

During re-breathing, two-way valve **68** is positioned to facilitate the flow of exhaled gases into and inhaled gases from deadspace **70**, which, after the patient has exhaled, includes gases from the patient's previously exhaled breath. The "during" phase preferably continues for about 50 seconds. The time at which the "during" phase occurs (t_D) is also determined. t_D may be calculated as the average time of the "during" phase, or otherwise, as known in the art, similar to the calculation of t_B.

After re-breathing, two-way valve **68** is repositioned to prevent the flow of gases through deadspace **70** as the patient breathes. The "after" phase may be of any duration sufficient to facilitate the accurate determination of VCO_2 and $CACO_2$. The time at which the "after" phase occurs (t_A) is also determined. t_A may be calculated as the average time of the "after" phase, or otherwise, as known in the art, similar to the calculation of t_B.

Referring again to FIG. **2**, and at reference **310** of FIG. **3**, the amount of carbon dioxide exhaled by the patient during each of the "before", "during" and "after" phases is detected by carbon dioxide sensor **14** (reference **74** of FIG. **1**) and monitored by CO_2 monitor **18**. CO_2 monitor **18** generates signals that, along with respiratory flow signals generated by flow monitor **16** in response to the flow of inhaled and exhaled gases by flow sensor 12, may be employed to determine VCO_2, at reference **340** of FIG. **3**, and the end tidal CO_2 partial pressure, at reference **320** of FIG. **3**, as known in the art. At reference **330** of FIG. **3**, the end tidal CO_2 partial pressure, which is assumed to estimate the partial pressure of carbon dioxide in the alveolar or end-capillary blood ($Pc'CO_2$) of the patient, may be employed with a carbon dioxide dissociation curve of a type known in the art to determine $CACO_2$.

The difference between the volume of carbon dioxide exhaled and the volume of carbon dioxide that is inhaled by a patient, which estimates the carbon dioxide elimination (VCO_2) of the patient, is determined before ($VCO_{2\ B}$), during ($VCO_{2\ D}$), and after ($VCO_{2\ A}$) re-breathing. FIG. **4** is a graph that illustrates VCO_2 during each of the before, during, and after phases of the re-breathing process of the present invention.

The partial pressure of end tidal carbon dioxide ($PetCO_2$ or $etCO_2$) is also measured for each of the "before", "during" and "after" phases. As $etCO_2$, when corrected for parallel deadspace (of non-perfused alveoli), is assumed to be equal to the partial pressure of CO_2 in the alveoli ($PACO_2$) and the partial pressure of CO_2 in the arteries ($PaCO_2$), a carbon dioxide dissociation curve may be employed with the end tidal carbon dioxide partial pressure measurements, as known in the art, to determine the content of carbon dioxide in blood of the alveoli ($CACO_2$) of the lungs of the patient that participate in the exchange of blood gases, which alveoli are typically referred to as "perfused" alveoli, for each of the before, during, and after re-breathing phases. $CACO_2$ is assumed to be equal to the content of carbon dioxide in the arterial blood ($CaCO_2$). FIG. **5** is a graph that illustrates the $etCO_2$ measured during each of the before, during, and after phases of the re-breathing process of the present invention.

Determining Pulmonary Capillary Blood Flow

In using the equations of the present invention to determine the pulmonary capillary blood flow or the cardiac output of a patient when $CvCO_2$ changes, the differences between the carbon dioxide elimination before re-breathing and during re-breathing, which difference is also referred to as "$\Delta VCO_{2\ BD}$", and during re-breathing and after re-breathing, which difference is also referred to as "$\Delta VCO_{2\ DA}$", are determined. The differences between the content of carbon dioxide in the alveolar blood before and during re-breathing, which difference is also referred to as "$\Delta CACO_{2\ BD}$", and during re-breathing and after re-breathing, which difference is also referred to as "$\Delta CACO_{2\ DA}$", are also determined.

These differences are then employed, at reference **350** of FIG. **3**, to calculate the rate at which the content of carbon dioxide in the venous blood of the patient changes. An exemplary equation for estimating the rate of change in the content of carbon dioxide in the patient's venous blood (k), which assumes that the change is linear with time and, therefore, that the rate of change is constant, follows:

$$k = \frac{\Delta V_{CO_{2BD}} \cdot \Delta C_A CO_{2DA} - \Delta V_{CO_{2DA}} \cdot \Delta C_A CO_{2BD}}{\Delta V_{CO_{2BD}} (t_D - t_A) - \Delta V_{CO_{2DA}} (t_B - t_D).} \quad (14)$$

Once the rate of change in the content of carbon dioxide in the patient's blood has been estimated, the pulmonary capillary blood flow of the patient may be accurately determined, at reference **360** of FIG. **3**, as follows:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2V_{CO_{2D}}}{k \cdot (t_B + t_A - 2t_D) - (C_A CO_{2B} + C_A CO_{2A} - 2C_A CO_{2D})} \quad (8)$$

Alternatively, the times and constant may be omitted from the previous equation and Q_{pcbf} or cardiac output of the patient determined by use of the following equation, which

is useful when either $CvCO_2$ or cardiac output changes during re-breathing:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2V_{CO_{2D}}}{-(C_ACO_{2B} + C_ACO_{2A} - 2C_ACO_{2D}).} \quad (9)$$

The intrapulmonary shunt flow of the patient or intrapulmonary shunt fraction of the cardiac output of the patient may also be determined, as known in the art, at reference **370** of FIG. **3**. The cardiac output of the patient may then be determined, at reference **380** of FIG. **3**, from the pulmonary capillary blood flow and intrapulmonary shunt flow of the patient, as known in the art.

Although the foregoing description contains many specifics, these should not be construed as limiting the scope of the present invention, but merely as providing illustrations of some of the presently preferred embodiments. Similarly, other embodiments of the invention may be devised which do not depart from the spirit or scope of the present invention. Features from different embodiments may be employed in combination. The scope of the invention is, therefore, indicated and limited only by the appended claims and their legal equivalents, rather than by the foregoing description. All additions, deletions and modifications to the invention as disclosed herein which fall within the meaning and scope of the claims are to be embraced thereby.

What is claimed is:

1. A method for non-invasively determining pulmonary capillary blood flow of a patient while a cardiac output or a carbon dioxide content of venous blood of the patient is changing, comprising:

measuring a before re-breathing carbon dioxide elimination and a before re-breathing partial pressure of end tidal carbon dioxide prior to a re-breathing phase;

measuring a during re-breathing carbon dioxide elimination and a during re-breathing partial pressure of end tidal carbon dioxide during said re-breathing phase; and

measuring an after re-breathing carbon dioxide elimination and an after re-breathing partial pressure of end tidal carbon dioxide after said re-breathing phase.

2. The method of claim **1**, wherein said cardiac output of the patient changes during at least one of said measuring said before re-breathing carbon dioxide elimination and said before re-breathing partial pressure of end tidal carbon dioxide, said measuring said during re-breathing carbon dioxide elimination and said before re-breathing partial pressure of end tidal carbon dioxide, and said measuring said after re-breathing carbon dioxide elimination and said before re-breathing partial pressure of end tidal carbon dioxide.

3. The method of claim **1**, wherein said cardiac output of the patient changes between said measuring before re-breathing and said measuring during re-breathing.

4. The method of claim **1**, wherein the cardiac output of the patient changes between said measuring during re-breathing and said measuring after re-breathing.

5. The method of claim **1**, wherein a venous content of carbon dioxide of the patient changes during at least one of said measuring before re-breathing, said measuring during re-breathing and said measuring after re-breathing.

6. The method of claim **1**, wherein a venous content of carbon dioxide of the patient changes between said measuring before re-breathing and said measuring during re-breathing.

7. The method of claim **1**, wherein a venous content of carbon dioxide of the patient changes between said measuring during re-breathing and said measuring after re-breathing.

8. The method of claim **1**, further comprising:

determining a before re-breathing alveolar content of carbon dioxide from said before re-breathing partial pressure of end tidal carbon dioxide;

determining a during re-breathing alveolar content of carbon dioxide from said during re-breathing partial pressure of end tidal carbon dioxide; and

determining an after re-breathing alveolar content of carbon dioxide from said after re-breathing partial pressure of end tidal carbon dioxide.

9. The method of claim **1**, further comprising:

determining a before time of said before re-breathing partial pressure of end tidal carbon dioxide;

determining a during time of said during re-breathing partial pressure of end tidal carbon dioxide; and

determining an after time of said after re-breithing partial pressure of end tidal carbon dioxide.

10. The method of claim **8**, further comprising calculating pulmonary capillary blood flow with said before re-breathing carbon dioxide elimination, said during re-breathing carbon dioxide elimination, said after re-breathing carbon dioxide elimination, said before re-breathing alveolar content, said during re-breathing alveolar content, and said after re-breathing alveolar content.

11. The method of claim **4**, further comprising calculating pulmonary capillary blood flow by employing the following equation:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2V_{CO_{2D}}}{-(C_ACO_{2B} + C_ACO_{2A} - 2C_ACO_{2D}).}$$

12. A method for non-invasively determining a pulmonary capillary blood flow of a patient while a cardiac output or a carbon dioxide content of venous blood of the patient is changing, comprising:

determining a before re-breathing carbon dioxide elimination ($VCO_{2\ B}$) of the patient and before re-breathing alveolar partial pressure of carbon dioxide ($PACO_{2\ B}$) of the patient;

re-breathing to determine a during re-breathing carbon dioxide elimination ($VCO_{2\ D}$) of the patient and during re-breathing alveolar partial pressure of carbon dioxide ($PACO_{2\ D}$) of the patient; and

determining an after re-breathing carbon dioxide elimination ($VCO_{2\ A}$) of the patient and after re-breathing alveolar partial pressure of carbon dioxide ($PACO_{2\ A}$) of the patient.

13. The method of claim **12**, further comprising calculating pulmonary capillary blood flow by the following equation:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2V_{CO_{2D}}}{-(C_ACO_{2B} + C_ACO_{2A} - 2C_ACO_{2D}).}$$

14. A method of non-invasively determining a pulmonary capillary blood flow of a patient while a cardiac output or a carbon dioxide content of venous blood of the patient is changing, comprising:

measuring a carbon dioxide elimination (VCO_2) of the patient before, during and after a re-breathing process; and

determining an alveolar partial pressure of carbon dioxide ($PACO_2$) of the patient before, during and after said re-breathing process.

15. The method of claim **14**, further comprising calculating pulmonary capillary blood flow (Q_{pcbf}).

16. The method of claim **15**, wherein said calculating pulmonary capillary blood flow comprises employing the following equation:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2V_{CO_{2D}}}{-(C_ACO_{2B} + C_ACO_{2A} - 2C_ACO_{2D}).}$$

17. A method for non-invasively determining pulmonary capillary blood flow of a patient while a cardiac output or a carbon dioxide content of venous blood of the patient is changing, comprising:

measuring a before carbon dioxide elimination and a before partial pressure of end tidal carbon dioxide prior to a change in effective ventilation;

measuring a during carbon dioxide elimination and a during partial pressure of end tidal carbon dioxide during said change in effective ventilation; and

measuring an after carbon dioxide elimination and an after partial pressure of end tidal carbon dioxide after said change in effective ventilation.

18. The method of claim 17, wherein said change in effective ventilation comprises re-breathing.

19. The method of claim 17, wherein a change in the cardiac output of the patient occurs during at least one of said measuring before said change in effective ventilation, said measuring during said change in effective ventilation, and said measuring after said changce in effective ventilation.

20. The method of claim 17, wherein a change in the cardiac output of the patient occurs between said measuring before said change in effective ventilation and said measuring during said change in effective ventilation or between said measuring during said change in effective ventilation and said measuring after said change in effective ventilation.

21. The method of claim 17, wherein said change in effective ventilation comprises a change in a respiratory rate.

22. The method of claim 17, wherein said change in effective ventilation comprises a change in an inspiratory time.

23. The method of claim 17, wherein said change in effective ventilation comprises a change in an expiratory time.

24. The method of claim 17, wherein said change in effective ventilation comprises a change in a tidal volume.

25. The method of claim 17, wherein said change in effective ventilation comprises a change in a quantity of carbon dioxide.

26. The method of claim 17, further comprising determining a rate of change of the carbon dioxide content of venous blood of the patient.

27. The method of claim 26, further comprising:

determining the before alveolar content of carbon dioxide from said before partial pressure of end tidal carbon dioxide;

determining a during alveolar content of carbon dioxide from said during partial pressure of end tidal carbon dioxide; and

determining an after alveolar content of carbon dioxide from said after partial pressure of end tidal carbon dioxide.

28. The method of claim 27, further comprising:

determining a before time of said before carbon dioxide elimination;

determining a during time of said during carbon dioxide elimination; and

determining an after time of said after carbon dioxide elimination.

29. The method of claim 26, further comprising:

determining a before time of said before partial pressure of end tidal carbon dioxide;

determining a during time of said during partial pressure of end tidal carbon dioxide; and

determining an after time of said after partial pressure of end tidal carbon dioxide.

30. The method of claim 27, further comprising: calculating said rate of change by employing the following equation:

$$k = \frac{\Delta V_{CO_{2BD}} \cdot \Delta C_ACO_{2DA} - \Delta V_{CO_{2DA}} \cdot \Delta C_ACO_{2BD}}{\Delta V_{CO_{2BD}}(t_D - t_A) - \Delta V_{CO_{2DA}}(t_B - t_D),}$$

where $\Delta VCO_{2\ BD}$ comprises a difference between said before carbon dioxide elimination and said during carbon dioxide elimination, $\Delta CACO_{2\ DA}$ comprises a difference between said during alveolar content and said after alveolar content, $\Delta VCO_{2\ DA}$ comprises a difference between said during carbon dioxide elimination and said after carbon dioxide elimination, $\Delta CACO_{2\ BD}$ comprises a difference between said before alveolar content and said during alveolar content, t_B comprises a time prior to said change, t_D comprises a time during said change, and t_A comprises a time after said change.

31. The method of claim 27, further comprising calculating pulmonary capillary blood flow with said before carbon dioxide elimination, said during carbon dioxide elimination, said after carbon dioxide elimination, said before alveolar content, said during alveolar content, said after alveolar content, and said rate of change.

32. The method of claim 28, further comprising calculating pulmonary capillary blood flow with said before carbon dioxide elimination, said during carbon dioxide elimination, said after carbon dioxide elimination, said before alveolar partial pressure, said during alveolar partial pressure, said after alveolar partial pressure, said before time, said during time, said after time, and said rate of change.

33. The method of claim 31, further comprising calculating pulmonary capillary blood flow by employing the following equation:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2V_{CO_{2D}}}{k \cdot (t_B + t_A - 2t_D) - (C_ACO_{2B} + C_ACO_{2A} - 2C_ACO_{2D}).}$$

34. The method of claim 26, wherein said rate of change is substantially constant.

35. The method of claim 26, wherein said rate of change is substantially exponential over time.

36. The method of claim 17, further comprising:

determining a before time of said before carbon dioxide elimination;

determining a during time of said during carbon dioxide elimination; and

determining an after time of said after carbon dioxide elimination.

37. The method of claim 36, wherein a difference between said during time and said before time is equal to a difference between said after time and said during time.

38. The method of claim 37, further comprising calculating pulmonary capillary blood flow by employing the following equation:

$$Q_{pcbf} = \frac{V_{CO_{2B}} + V_{CO_{2A}} - 2V_{CO_{2D}}}{-(C_ACO_{2B} + C_ACO_{2A} - 2C_ACO_{2D}).}$$

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,210,342 B1
DATED : April 3, 2001
INVENTOR(S) : Kai Kück and Joseph A. Orr

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [56], **References Cited**, OTHER PUBLICATIONS,
In "Miller, D.M., et al." change "Estimated" to -- Estimate --
In "Österlund, B., et al." change "Act" to -- Acta --

Column 7,
Lines 7 and 23, after the first equation and before the second equation, insert -- or --

Column 8,
Line 8, change "fote" to -- form --

Column 10,
Line 21, before "Accordingly" change "re-breathing," to -- re-breathing. --

Signed and Sealed this

Twenty-second Day of July, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office